In order to expedite prosecution, applicants have amended the specification in order to incorporate by reference certain subject matter the Examiner requested. This material is that set forth in the references cited and as such does not constitute new matter. Accordingly, its entry is respectfully requested.

Applicants have amended the claims to incorporate the recitation of claim 2 into claim 1. Applicants also amended the claims in order to correct a minor typographical error that is grammatical in nature and is supported by the specification at page 15. And have rewritten claim 9 to make it clearer. As such these amendments do not constitute new matter and their entry is respectfully requested.

Applicants note that while they added certain matter requested by the Examiner to the specification they have done so voluntarily, not because they agree with the Examiner that such material constitutes essential material. Rather, applicants submit that the application and claims are directed to those of skill in the art. Thus, applicants submit that from the teaching provided herein, even without the material requested, the specification taught those of ordinary skill in the art how to practice the invention. In two instances applicants did not make the incorporations by reference requested. The first case, applicants did not incorporate by reference the specific nucleotide sequence of the human protamine gene. That is because from the information the specification provided, particularly the example at page 25, the use of protamine is clearly enabled. The Examiner has stated that the particular plasmid used may not be available. However, applicants point out that page cited a reference that provided the specific nucleotide sequence of the gene and how it was inserted into said plasmid. See, Figures 1 and 3 and the accompanying text of Krawetz, et al., *Genomic* 5:639-645 (1989) (copy attached). Accordingly, applicants respectfully submit that regardless of the availability of the

plasmid, from the information available to those of ordinary skill in the art, based upon the exemplification provided herein, one could readily prepare a fusion protein having a human protamine portion.

With respect to the TFII S nucleic acid binding domain, applicants respectfully submit that they provided in the specification information in a sufficient form for those of ordinary skill in the art, namely referring to it as the C terminal residues 231-280. This terminology was sufficient to identify the region in Qlan, et al. *Nature* 365:277-279 (1993). This journal is a peer-reviewed journal and the degree of detail provided therein indicates what the art accepts as sufficient for identifying a particular region at the time this application was filed. This journal, as do most such journals, does not require one to list nucleotide sequences when they are readily available to those of skill in the art providing there is sufficient guidance in the article. Applicants respectfully submit that there was sufficient guidance herein and that the inclusion of the specific nucleotides would be unnecessary to those of skill in the art to practice this invention. Accordingly, the inclusion of such nucleotide information is not necessary to practice the invention.

Applicants also believe that it is not necessary with respect to the other references but in order to expedite prosecution have provided it.

Claims 1-16 were rejected under 35 U.S.C. §112, first paragraph.

Applicants respectfully submit that the discussion with respect to the necessity of listing nucleotide sequences based upon the disclosure herein as essential matter, indicates that the specification does not have to explicitly disclose amino acid

and nucleotide sequences. Rather, these references show that there is certain terminology that is well known to those skilled in the art and that by applicants teaching how it can be used, one can readily practice the invention. Applicants have shown how the gene delivery system can be made and used. One can readily reproduce these techniques and readily adapt these techniques to other techniques. Applicants have shown how PCR technique can be used to amplify preferred DNA fragments and one can readily apply such teaching to use numerous nucleotide sequences. Thus, one would readily be able to make the exemplified constructs.

For example, applicants have obviated most of this rejection by the inclusion of certain information and others are readily available by terminology used herein, e.g., the identification of the nucleotide sequence of the protamine gene (See, for example, Figure 1 of Krawetz, et al., *Genomic 5*, a copy of which is attached hereto). Indeed, the references relied upon by the Examiner, with respect to 103 rejection, similarly show how the disclosure by applicants is in accord with that which is used in the art for exemplification purposes.

Applicants respectfully submit that the Examiner's contention that the specification does not adequately teach how to use the claimed method for *in vivo* application tries to read into a claim a requirement that is not there and therefore tries to impose a standard that it higher than that required by case law or the Office. Claim 1, for example, is directed to a nucleic acid delivery system. Claim 13 is directed to a method of transforming a target cell. Claim 14 is directed to a method of preparing a nucleic acid delivery system. None of these claims are directed *per se* to a therapeutic composition. As applicants teach, the nucleic acid delivery system can be used for a wide range of purposes, including the delivery of markers.

Furthermore, the Examiner concedes that it is "not unreasonable" to expect that the transfer of polynucleotides would be achieved at least to some extent. In other words, the Examiner has conceded that it is reasonable to believe that the gene delivery system claimed herein will work as taught. The Examiner argued, however, that since the claims are directed to an *in vivo* use, that requires a higher degree of transformation that *in vitro* use would require. However, *in vivo* uses include cell labelling, somatic cell therapy, whereby one can readily screen for those cells that have been transformed by the present system and readministered only those transformed cells. Thus, by the Examiner's own admission, in these instances at least, it is reasonable to believe that the invention would work as taught.

With respect to the Examiner's statement from Curiel, applicants do not believe that the Examiner is reading it right. Regardless, applicants submit that to require applicants to provide utility for **all** uses is not necessary. The Office has made clear in the recent final Utility Guidelines that they apply to both rejections under 35 U.S.C. §101 and §112. And, the Guidelines make clear that teaching satisfactory for **one** use is sufficient. Thus, the Examiner's argument that they must prove that the nucleic acid delivery system work in all uses, imposes a burden that is not there.

Indeed, the Examiner's argument that applicants must establish that the claim compositions could reach all cell types ignores what is being claimed. What is being claimed is a nucleic acid delivery system, not a method of targeting brain cells. Nevertheless, even if the Examiner has assumed something that is not there, that the fusion proteins of the present invention must be able to be used to target brain cells, one could use various techniques such as microcatheters and other means to place these nucleic acid delivery system vectors near

the desired cells and then let them target the appropriate ones without concern about the blood brain barrier.

Indeed, the Curiel and Wu references show applicants invention would not require undue experimentation for numerous applications.

These are not claims that are directed to a method of treating specific cells, but for example, claims to a unique gene delivery system and the use of this nucleic acid delivery system. Thus, the standard imposed is the wrong one.

Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claims 6, 9, 13, 15 and 16 were rejected under 35 U.S.C. §112, second paragraph.

Applicants respectfully submit that the rejection to claim 6 is improper as applicants believe it is clear that where family members are recited, those family members are included.

Applicants respectfully submit that the use of the language in claim 9 was clear in that it taught that the nucleic acid segment has both a flanking 5′ and 3′ LTR (or ITR) region, i.e. that the nucleic acid sequence itself was flanked at either end by these regions. However, applicants respectfully submit that the amendment to the claim has clarified this and also obviate the other rejection to claim 9.

Applicants believe that it is clear to the skilled artisan that one is talking about flanking the promoter and gene(s) at one end with a 5′ LTR or ITR and at the other end with a 3′ LTR or ITR.

Applicants respectfully submit that the Examiner's objection to claims 13, 15 and 16 as being confusing because they imply *in vitro* use of the methods is inappropriate because as noted the present claims encompass the use of somatic cell therapy. Furthermore, applicants note that it was the Examiner who issued a restriction requirement to the exact same claims between *in vitro* and *in vivo* applications. If the Examiner believed that certain claims were more appropriately directed to *in vitro* use than *in vivo* use, the Examiner should have restricted such claims out at that time. Applicants believe that any difficulty encountered with such claims is not a difficulty in the way they are worded but in the artificiality of the restriction requirement. Not only does this language encompass somatic cell therapy, where cells are removed to a particular medium, but it contemplates direct administration of cells that are not removed. As noted, one can administer the nucleic acid delivery system by any other number of means directly to locations inside the body.

Accordingly, applicants respectfully submit that this objection to the claims should be withdrawn.

With respect to the Examiner's objection to the use of the term "waiting until", applicants respectfully submit that the skilled artisan can readily determine when that event has occurred and that in this field, there is sufficient guidance to wait the appropriate time. This time will vary and depend upon what is being administered, the method that it administered, the cell transduced, and such results can readily be determined empirically by those of skill in the art. Thus, the fact that a set time period is not listed, does not indicate that the claim is indefinite but rather, is appropriate for this type of claim. Accordingly, applicants respectfully request that the Examiner reconsider the objection to this language.

Claims 1, 8, and 9 were rejected pursuant to 35 U.S.C. §102(b) as being anticipated by Beug, et al.

In order to expedite prosecution, applicants have amended the claims to the preferred embodiment, wherein the targeting moiety is an antibody without prejudice to refiling claims directed to other targeting moieties.

Claims 2-5, 7 and 10-16 were rejected under 35 U.S.C. §103 as being unpatentable over Beug, et al. in view of Chaudhary, et al. and Wu, et al.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Except by hindsight, there is nothing that would suggest the nucleic acid delivery system such as that claimed by the present invention. Substantially, most of Beug and all of Wu are directed to the use of chemically synthesized conjugates. Thus, the combination of these two references would not teach preparing a fusion protein but rather suggests that combining different moieties chemically is preferred.

Secondly, Beug does not teach the use of antibodies to target different moieties but is directed to using a totally different compound, transferrin. The targeting moiety Wu used was also limited and directed to targeting a particular type of receptor, i.e. an asialoglycoprotein receptor, which is exemplified by hepatic cells, such as the liver cell. This was exemplified not by use of an antibody, but rather, also by a ligand that would bind to the receptor, for example, the protein orosomucoid. Thus, the combination of Beug and Wu do not in any way suggest the inclusion of an antibody as part of the targeting moiety and therefore the addition of Chaudhary to this combination in no way suggests that one should use an antibody

instead of such a ligand. Particularly, since Chaudhary doesn't talk about delivering **DNA** to specifically targeted cells. Thus, when the three references are read together, except by hindsight, one would be lead **not** to use antibodies but rather other ligand to receptors. Certainly, there was nothing that would teach the use of numerous types of antibodies when these are so specific.

Nor is there anything that teaches the desirability that such compositions should be fusion proteins for a nucleic acid delivery system. Accordingly, except by hindsight picking and choosing from these different references, there is nothing in these references that teaches the desirability of fusing a DNA binding moiety to an antibody targeting moiety. The U.S. Court of Appeals for the Federal Circuit has cautioned time and again of the dangers of trying to pick portions from references when there is no blueprint in the reference that teaches the claimed invention. Yet, this is precisely what has been done by stating one portion of a reference teaches the desirability of one combination, while ignoring the broad teaching of the **entire** reference. Accordingly, applicants respectfully submit that this rejection should be withdrawn.

Claim 6 was rejected under 35 U.S.C. §103 as being unpatentable over Beug, et al. and Chaudhary, et al. and Wu, et al. as applied above and further in view of Ryder, et al.

Applicants respectfully submit that the addition of Ryder, et al. to the combination in no way overcomes the essential deficiency of the combinations discussed above of. Accordingly, for the reasons mentioned above, which are repeated herein, this rejection of the claims should also be withdrawn.

In view of the foregoing, applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

Respectfully submitted,

By: Ronald I. Eisenstein

Ronald I. Eisenstein
Reg. No. 30,268

(617) 523-3400
Dike, Bronstein, Roberts & Cushman
130 Water Street
Boston, MA 02109